How AMPA Receptors Conduct Ions

The Influence of Different Ions and Auxiliary Subunits on the Ion Conduction Behavior of AMPA-type Glutamate Receptors

F. Heiser[1,2], H. Sun[2,3], A. Plested[1,2], *[1]Humboldt-Universität zu Berlin, [2]Leibniz-Forschungsinstitut für Molekulare Pharmakologie, [3]Technische Universität Berlin*

In Short

- AMPAR ion conduction is regulated by many factors
- MD simulation is applied to elucidate the mechanisms behind ion gating and conduction
- Q/R editing in the selectivity filter combined with different ion mixtures as well as the influence of auxiliary proteins are the focus of this work

Ionotropic glutamate receptors are ligand gated ion channels located in post synaptic membranes in the central nervous system. Part of this superfamily are the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) which are known for their exceptionally fast synaptic currents and receptor kinetics. They are tetrameric receptors as shown in figure 1. AMPARs exhibit a variety of interesting regulation mechanisms with which they are large contributors to synaptic plasticity. The molecular details of most of these mechanisms remain unclear up to date. One striking feature of the AMPARs are the agonist concentration dependent sub-conductance states[1]. The AMPAR ion channel opens up to sub levels depending on how many glutamates bind to the receptor. This leads to conductances lower than the fully in open state. The ion conduction mechanism behind these sub-conductances is rather unclear and needs elucidation with the aid of molecular dynamics (MD) simulations. Unclear as well is the mechanism of the effect of so called TARPs (transmembrane AMPAR regulatory proteins) which are a group of proteins that bind to the transmembrane domain of the AMPA receptor. They can have different effects from inhibiting desensitisation to influencing the ion conductance or the opening state of the receptor[2]. Here too, MD simulation will help to shed light on the molecular mechanisms on an atomistic scale with pico second temporal resolution. Furthermore, the ion selectivity of the AMPAR is interesting. While being rather unselective to monovalent cations, the calcium conductance relies on a specific amino acid in the selectivity filter. Due to a post transcriptional editing site there is either a Q or an R in this certain position, while the Q-edited form is calcium permeable and the R-edited form is impermeable to divalent cations. Because AMPARs are tetramers, up to four Qs can be replaced by an R. The question is, whether the calcium conductance is gradually reduced by successively introducing Rs to the selectivity filter and how a physiological mixture of different ions influences the conductance of calcium. The last interesting question we want to tackle in this project regards the ability of AMPARs to be blocked by polyamines. TARPs influence the polyamine block and the underlying molecular mechanism remains obscure.

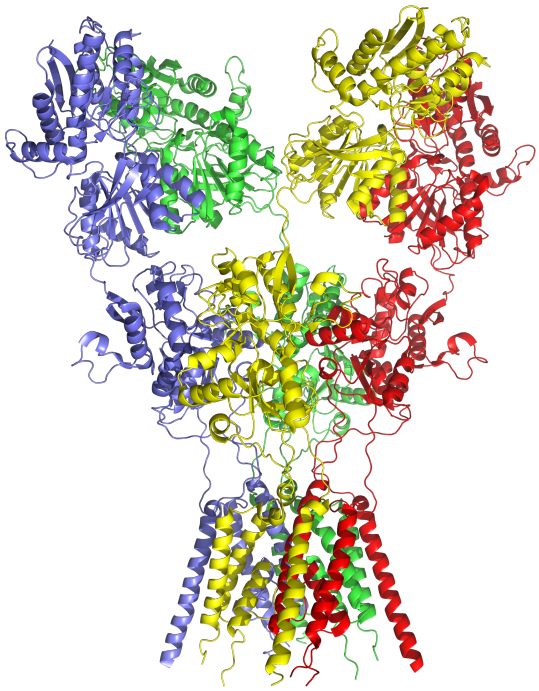

Figure 1: *The AMPA core receptor assembles as a tetramer with three major domains (from top to bottom): aminoterminal domain, ligand binding domain and transmembrane domain*

Different cryo-EM structures of AMPARs are available to serve as starting point for MD simulations. With the focus on the ion conduction pathway we want to find out what the influences of different ion mixtures and TARPs are and how they can be explained on an atomistic level. In order to clarify all of these questions within this project, we use the so called "computational electrophysiology" aproach[3]. Figure 2 shows exemplarily how a typical simulation system looks like. Two lipid bilayers with a copy of the ion channel embedded in each of them divide the simulation box in two compartments. An

ion imbalance is maintained throughout the simulation, resulting in an transmembrane potential which drives the ions through the channel. Inward and outward flow of the ions through the channel can be simulated simultaneaously.

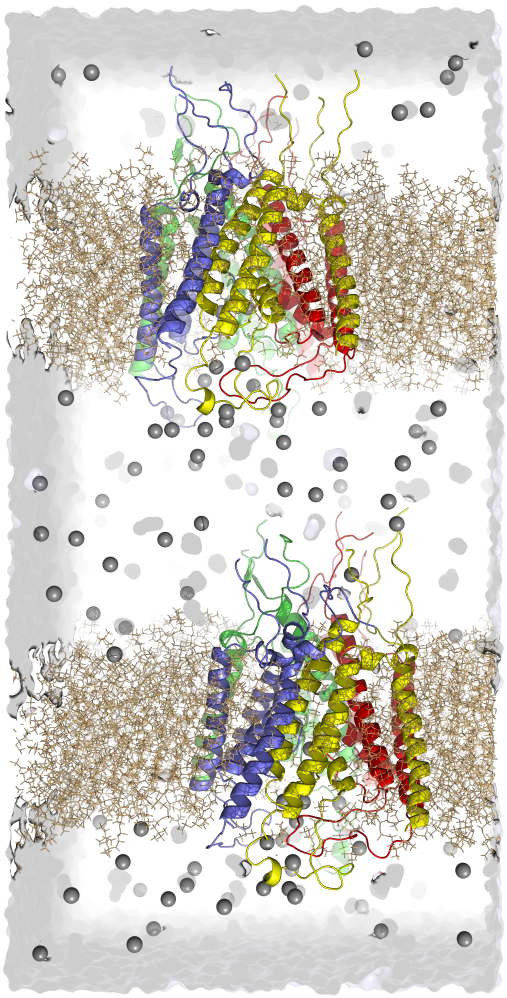

Figure 2: *Computational electrophysiology system containing two membranes with the AMPAR transmembrane domain embedded. Grey spheres are cations, anions and water are not shown.*

To save computational costs it is important to keep the number of atoms in the simulation box as small as possible. This is why only the ion channel pore containing transmembrane domain of the AMPAR is simulated. Position restrains are applied to the linkers to the cut off ligand binding domain.

WWW

https://www.leibniz-fmp.de/de/plested
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More Information

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